Remarks

I. Addressing The Examiner's Rejection of Claims 11, 12, 24, 28, 33, 39 and 40 under 35 U.S.C. §112, First Paragraph.

The Examiner rejected claims 11, 12, 24, 28, 33, 39 and 40 under 35 U.S.C. §112, first paragraph, asserting (i) that the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration Onyx 051 and 053 (comprises a single amino acid substitution in amino acid 240 or 260), does not reasonably provide enablement for any other embodiment, and (ii) that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

A. Applicants Submit the Specification Provides Enablement Commensurate in Scope with the Claimed Subject Matter.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See Ex Parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). A patent may be enabling even though some experimentation is necessary. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir. 1988).

In the present application, applicants have clearly enabled one of ordinary skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation for the following reasons:

(i) The Examiner has acknowledged that the efficacy of the present invention lies in the treatment of p53(-) tumors (*see, e.g.,* specification, Example 4, page 23) and that the efficacy of combined adenoviral/chemotherapy treatment has been specifically observed, for example, as discussed by Kim, et al. (*see* Office action, mailed 15 January 2008, paragraph bridging pages 3-4). Further, the Examiner has acknowledged the efficacy of the methods of the present invention by indicating allowable subject matter (*see* Office action, mailed 15 January 2008, page 8).

(ii) Applicants' specification explicitly describes the methodology for the creation of the recombinant adenovirus of the present invention as well as methods of identifying recombinant adenoviruses having the desired characteristics for use in the practice of the methods of the present invention.

(iii) Finally, the Examiner's asserted scope rejection regarding enablement of embodiments other than Onyx 051 and 053 is completely inconsistent with the fact that the recombinant adenovirus recited in the independent claims of the present application mirrors the claim limitations in the independent claims that recited the same recombinant adenovirus of the granted patent of the parent application.

The Examiner has not taken issue with enablement of any of the dependent claims and has focused arguments only on the elements of the independent claims. There are two pending independent claims -- claims 11 and 33. Claim 33 primarily differs from claim 11 in that claim 33 comprises "administering by direct injection into the tumor a dose of a recombinant adenovirus" and claim 11 comprises "administering to said patient a dose of a recombinant adenovirus." Accordingly, the following arguments, although focused on the limitations of claim 11, are equally applicable to the limitations of claim 33.

The Examiner's rejection focuses on the assertion that applicants' claims include "broad recitation of a genus of adenovirus for delivery to p53 lacking neoplastic cells wherein the adenovirus have reduced binding to p53" (*see* Office action, 15 January 2008, page 4).

The focus of the Examiner's rejection is further illustrated in the following remarks:

> However, by recitation that the rAd comprises a single amino acid mutation in EIB-55K, the adenovirus to be used in the treatment encompasses a broad and diverse genus of adenoviruses that need only be linked by a mutation in EIB-55K. Rather the nature of the adenoviruses for treatment of cancer according to the instant invention must be replicative. To this end, applicants generated 26 mutants but only two of these mutants are capable of reduced binding to p53. These mutants (Onyx 051 and 053) comprise a single mutation in amino acid 240 and 260.
>
> Hence, applicants have elucidated the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26 produced have the recited functional requirements. As well, applicants have not provided the structural requirements of the single amino acid mutants such that one of skill in the art would be able to identify those mutants that have lost the ability to bind efficiently to p53. **Hence, the unpredictability of using the claimed invention in gene therapy is accentuated due to the broad and unpredictable nature of the identifying adenovirus with single amino acid mutations in the E1B 55k gene that have lost the ability to bind p53 and furthermore be used to treat cancer.** (*See* Office action, mailed 15 January 2008, pages 4-5; emphasis added.)

The Examiner has not presented any evidence to support the Examiner's assertion that "the unpredictability of using the claimed invention in gene therapy is accentuated due to the broad and unpredictable nature of the identifying adenovirus with single amino acid mutations in the E1B 55k gene that have lost the ability to bind p53 and furthermore be used to treat cancer." This is no more than a conclusionary statement. Applicants, on the other hand, have presented extensive evidence that counters the Examiner's assertion of "unpredictability."

First, the Examiner has acknowledged that the efficacy of the present invention lies in the treatment of p53(-) tumors and that the efficacy of combined adenoviral/chemotherapy treatment have been specifically observed, for example, as discussed by Kirn, et al. (*see* Office action, mailed 15 January 2008, paragraph bridging pages 3-4). Further, the Examiner has acknowledged the efficacy of the claimed methods of treating cancer by indicating allowable subject matter (*see* Office action, mailed 15 January 2008, page 8).

Kirn, et al., discuss the use of adenovirus mutant *dl*1520 (ONYX-015) in clinical trials for the treatment of a number of cancer types. As discussed by Kirn, et al.:

> *dl*1520 (Onyx-015) was the first adenovirus described to mirror the gene deletion approach pioneered by Martuza with herpesvirus. Bischoff *et al.* (1996) hypothesized that an adenovirus with deletion of a gene encoding a p53-binding protein, E1B-55 kD, would be selective for tumors that already had inhibited or lost p53 function. p53 function is lost in the majority of human cancers through mechanisms including gene mutation, overexpression of p53-binding inhibitors (e.g., mdm2, human papillomavirus E6) and loss of the p53-inhibitory pathway modulated by $p14^{arf}$. (Kirn, et al., page 6653, col. 1.)

Kirn, et al., provide extensive discussion of the use of adenovirus ONYX-015 alone and in combination with chemotherapy for the treatment of cancer. Kirn, et al., state the following with regard to ONYX-015:

> For the first time since viruses were first conceived as agents to treat cancer over a century ago, we now have definitive data from numerous phase I and phase II clinical trials with a well-characterized and well-quantitated virus. *dl*1520 (Onyx-015, now CI-1042, Pfizer, Inc.) is a novel agent with a novel mechanism of action. This virus was to become the first virus to be used in humans that had been genetically-engineered from replication-selectivity. (Kirn, et al., page 6664, col. 2).

Further, Kirn, et al., discuss the evidence for a potential-synergistic interaction between adenoviral therapy and chemotherapy that has been demonstrated in multiple clinical trials (Kirn, et al., page 6666, col. 1, to 6667, col. 1).

Kirn, et al., conclude:

> Replication-selective oncolytic adenovirus represent a novel cancer treatment platform. Clinical studies have demonstrated the safety and feasibility of the approach, including the delivery of adenovirus to tumors through the bloodstream (Heise *et al.*, 1999b; Reid *et al.*, 1999; Nemunaitis *et al.*, 1999). The inherent ability of replication-competent adenoviruses to sensitize tumor cells to chemotherapy was a novel discovery that has led to chemosensitization strategies. (Kirn, et al., page 6667, col. 2).

In the present application, applicants have consistently compared important phenotypes of ONYX-015 to the replication-selective recombinant adenoviruses of the present invention. Applicants demonstrated that the recombinant adenoviruses of the present invention (i) showed substantially reduced binding of p53 (as does ONYX-015; *see* specification, Example 2, pages 19-22), (ii) showed protein synthesis profiles more similar to wild-type than to ONYX-015 which is an advantage because generally higher levels of adenoviral replication correspond to increased cytotoxicity in target cells (*see* specification, Example 3, pages 22-23), and, consistent with the previous observation, (iii) tumor cell specific cytolytic activity of the recombinant viruses of the present invention was higher than ONYX-015 (*see* specification, Example 4, page 23). Thus, it is clear from the data presented by applicants that the recombinant viruses of the present invention provide at least similar if not superior anti-cancer properties relative to ONYX-015, which has been demonstrated in clinical trials to be useful for the treatment of cancers.

One important previously unrecognized advantage of recombinant adenovirus of the present invention, comprising the single amino acid mutations, resides in the observation that recombinant adenoviruses comprising a single amino acid substitution mutation in the E1B-55K gene resulted in recombinant adenoviruses that had replication capacity in human cancer cells more like wild-type adenovirus versus the attenuated replication capacity of ONYX-015 (see, e.g., specification page 12, lines 10-20). This increased ability to replicate in human cancer cells results in improved tumor cytolytic activity relative to, for example, ONYX-015 (see, e.g., specification, page 23, lines 20-35).

Further, the present specification discusses the combination of the claimed recombinant adenoviruses with chemotherapy (see, e.g., specification, pages 16-17).

The Examiner has presented no evidence to support the assertion that use of the recombinant adenovirus of the present invention in a method of treating a cancer, characterized by neoplastic cells that substantially lack p53 function, is "unpredictable." As discussed above, the Examiner's assertions are contradicted by the teachings of the specification and the teachings of Kirn, et al.

Second, the Examiner asserts "applicants have elucidated the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26 produced have the recited functional requirements" (*see* Office action, mailed 15 January 2008, page 5). However, the specification contains extensive teachings regarding making of the recombinant adenoviruses used in the methods of the present invention.

Adenovirus E1B-55K protein sequences and nucleic acid coding sequences are well known in the art (*see, e.g.*, specification, pages 1-3; page 6, lines 7-10; page 9, lines 24-32; page 10, line 31 to page 11, line 19; page 12, lines 7-9; Example 1, pages 17-19). Specifically, the region of the E1B-55K protein that mediates its interaction with the p53 protein has been mapped (*see, e.g.*, specification, page 10, lines 31-34). Methods of constructing adenoviral mutants are known in the art (*see, e.g.*, specification, page 11, lines 15-28; page 12, lines 3-9). Guidance concerning substitution of amino acids suitable for generating mutant polypeptides is discussed in the specification (*see, e.g.*, specification, page 12, line 21, to page 13, line 23). Tumor cell lines used to conduct screening of recombinant adenovirus are readily available (*see, e.g.*, specification page 11, line 29, to page 12, line 2). A patent need not teach, and preferably omits, what is well known in the art. *See Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1453, 221 USPQ 481, 489 (Fed. Cir. 1984). *See Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d at 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

In addition, applicants have provided a disclosure that explicitly describes the methodology for the creation of the recombinant adenovirus of the present invention as well as methods of identifying recombinant adenoviruses having the desired characteristics for use in the practice of the methods of the present invention. Example 1 (*see* specification, pages 17-19) describes construction of twenty-five single amino acid substitution E1B-55K mutant

adenoviruses and one mutant having two amino acid substitutions. Each recombinant adenovirus was generated using a forward primer and a reverse primer. Final products were transformed into XL-1 cells and confirmed by DNA sequencing. Recombinant viruses were constructed by co-transfecting pJM17 with plasmids containing the mutations into 293 cells and were plaque purified to rule out wild-type contamination. Mutations were confirmed by PCR followed by sequencing of the E1B-55K region.

Example 2 (*see* specification, pages 19-22) describes evaluation of binding of the isolated E1B-55K mutants with p53. The twenty six mutant adenoviruses produced as described in Example 1 were initially screened to determine their effect on the steady-state levels of p53 in A549 cells. These data suggested that two of the adenoviral E1B-55K mutants, R240A and H260A fail to bind p53. This was confirmed by directly examining the ability of the E1B-55K mutants R240A and H260A to interact with p53 by immunoprecipitation experiments using S^{35}-labeled cell extracts from infected A549 cells.

Example 3 (*see* specification, pages 22-23) describes the effects of the E1B-55K mutations on the ability of the recombinant adenoviruses to replicate in target cells. The ability to replicate in target tumor cells generally improves the cytotoxicity of the recombinant adenovirus. At 39°C., all of the viruses replicated to similar extent. The yield of *dl*309 was approximately 4-fold higher than that of ONYX-015, and the yields of ONYX-051 (mutant R240A) and ONYX-053 (H260A) fell in between. At 32°C., however, the ONYX-015 yield was reduced nearly 35-fold compared to that of *dl*309, which is consistent with the previous reports. Replication of ONYX-051 was essentially identical to that of *dl*309, while replication of ONYX-053 was slightly reduced (4-fold). Thus ONYX-051 (mutant R240A) and ONYX-053 (H260A) have an improved ability to replicate in target cells relative to ONYX-015. Further, the protein synthesis profile in cells infected with ONYX-051 (mutant R240A) and ONYX-053 (H260A) was similar to that in cells infected with wild-type viruses *dl*309 and WtD. This observation suggests that ONYX-051 (mutant R240A) and ONYX-053 (H260A) are capable of modulating mRNA trafficking in favor of late viral mRNA nuclear export.

Example 4 (*see* specification, page 23) describes the cytotoxic activity of recombinant adenoviral E1B-55K mutants. Among the recombinant adenoviruses described in the application, most, including ONYX-051, were comparable to *dl*309 in their ability to infect

and kill tumor cells. In the case of ONYX-053, its tumor cytolytic activity was 35- to 100-fold lower than that of *dl*309, but more active than ONYX-015 by a factor of 4- to 5-fold.

Accordingly, two recombinant adenoviruses were identified out of twenty-six recombinant adenoviruses, using the methods described in the present application, that met the criteria for use in a method of treating cancer as outlined above and further were discussed relative ONYX-015, the use of which the Kirn, et al., reference discusses in the context of clinical trials for cancer treatment.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation *See Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). The law does not require the impossible. Hence, it does not require that an applicant describe in his specification every **conceivable** and possible future embodiment of his invention. *See SRI International v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577 (Fed. Cir. 1985); emphasis in original. Further, the enablement requirement may be satisfied even though some experimentation is required. *See Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

Accordingly, the specification describes in detail how to make recombinant adenoviruses comprising a single amino acid substitution mutation in the E1B-55K gene, how to determine that the mutation reduces the ability of the mutated E1B-55K protein to bind to the tumor suppressor p53, how to determine the recombinant adenoviruses that retain late viral function, and how to determine killing of neoplastic cells that substantially lack p53 function.

Applicants have taught one reasonably skilled in the art to make and use the invention from the disclosures in the application coupled, if necessary, with information known in the art without undue experimentation. Applicants described two specific embodiments of the recombinant adenoviruses of the present invention. It is it not required that applicants describe in the specification every **conceivable** and possible future embodiment of the invention.

Finally, applicants respectfully point out that application USSN 09/918,696, now U.S. Patent No. 6,635,244, is the parent application to the present application, was examined by the same Examiner, and comprises the following granted claims:

1. A recombinant adenovirus comprising a mutation in the E1B-55K gene, said gene encoding a mutated E1B-55K protein comprising a single amino acid mutation, said single amino acid mutation reducing the ability of said E1B-55K mutated protein to bind to the tumor suppressor p53 when compared to the wild-type E1B-55K protein and said adenovirus has the further property of retaining late viral function.

2. A recombinant adenovirus as described in claim 1, wherein said adenovirus is selected from the group consisting of Onyx 051 and Onyx 053.

3. A recombinant adenovirus as described in claim 2 wherein said adenovirus is Onyx 051.

4. A recombinant adenovirus as described in claim 2 wherein said adenovirus is Onyx 053.

5. A recombinant adenovirus as described in claim 1, wherein said adenovirus has a mutation in amino acid 240 or 260.

6. A recombinant adenovirus as described in claim 1, wherein the replication of said adenovirus is cold insensitive.

As the parent application is now an issued U.S. Patent, the presumption of validity under 35 U.S.C. §282 carries with it the presumption that the Examiner did the Examiner's duty and knew what claims the Examiner was allowing. The recombinant adenovirus in the independent claims of the present application mirror the claim limitations in the independent claims of the granted patent of the parent application. Accordingly, applicants submit that it is completely inappropriate for the Examiner to be questioning the scope of the presently claimed invention based on a question of whether or not one of ordinary skill in the art is capable of making or using the claimed recombinant adenovirus in a method of treating cancer. The claims of the granted parent application support that making of the required recombinant adenoviruses is enabled by the teachings of the present specification. The teachings of the present application, as further evidenced by the teachings of the reference of Kirn, et al., enable use of the claimed recombinant adenovirus in the methods of the present invention.

In the present application, applicants have isolated and characterized recombinant adenovirus comprising a single amino acid substitution mutation in the E1B-55K gene that reduces the ability of the mutated E1B-55K protein to bind to the tumor suppressor p53,

wherein the recombinant adenovirus retains late viral function. Applicants were the first to demonstrate that single amino acid mutations were capable of reducing or eliminating E1B-55K protein's ability to bind to the tumor suppressor p53 and that recombinant adenoviruses harboring such single amino acid mutations demonstrated tumor cytotoxicity.

In view of the above arguments, applicants submits that the claims are enabled for the entire scope of the claimed invention. Applicants respectfully request withdrawal of that the rejection of the claims under 35 U.S.C 112, first paragraph.

B. The Examiner Has Failed to Establish a Prima Facie Case of Lack of Enablement Commensurate in Scope with the Claimed Subject Matter.

To support the rejection of the claims for lack of enablement commensurate in scope with the claimed subject matter, the Examiner stated the following:

> The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, applicants recite use of a broad genus of adenovirus to treat cancer. The instant rejection is based upon the highly unpredictable nature of the claimed method of treatment of *any* cancer using *any* of a broad genus of adenovirus. The lack of guidance as to the molecules to be used exacerbates the highly unpredictable nature of treating cancer. While one of skill in the art can readily envision numerable species of nucleic acid sequences that have at least a single amino acid mutation in EIB 55k, one cannot predict which of these also generate an adenovirus that treats cancer. (*See* Office action, mailed 15 January 2008, page 6.)

In citing *Atlas Powder* and *In re Cook*, the Examiner has done nothing more than assert that the specification "does not clearly identify operative embodiments and undue experimentation is involved in determining those that are operative." On the other hand, as discussed herein above, the specification clearly teaches how to make and use the recombinant adenovirus of the present invention. Further, when confronted with a similar pattern of facts in the field of recombinant, molecular biology the Board of Patent Appeals and Interferences (B.P.A.I.) found that the Examiner had not established a reasonable basis

for questioning the sufficiency of the supporting disclosure when taken in combination with the relevant state of the art as it related to the claimed invention. In *Ex parte Chen*, 61 USPQ2d 1025 (B.P.A.I. Aug. 22, 2001) (unpublished) the invention as claimed was to a transgenic carp containing an exogenous gene encoding a growth hormone (the rtGH gene) that was operably linked to a promoter. This exogenous rtGH gene was introduced into the carp at an embryonic stage.

Certain claims were rejected by the Examiner who asserted the specification did not disclose a process that was repeatable as to the levels of expression to obtain carp or other fish that expressed the same transgene product, wherein the level of expression was shown to directly affect phenotypic characteristics of the fish. In support of the rejection, the Examiner cited a prior art reference as evidence of a level of unpredictability in this art. The reference taught that there are three steps or factors that must be shown to exist in a true transgenic animal: (1) integration into the host chromosome, (2) expression, and (3) germ-line transmission of foreign genes.

The applicant (Chen) did not dispute the three factor test presented by the Examiner but argued that the specification would meet this test and permit a person skilled in this art to make and use the claimed invention by following the detailed procedures disclosed in applicant's specification. *See Ex parte Chen*, 61 USPQ2d 1025, 1028 (B.P.A.I. Aug. 22, 2001) (unpublished).

Regarding the overall inquiry concerning enablement the B.P.A.I. stated the following:

> We are mindful that the Patent and Trademark Office (PTO) bears the initial burden of providing reasons for doubting the objective truth of the statements made by appellants as to the scope of enablement. Only when the PTO meets this burden, does the burden shift to appellants to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. *See Ex parte Chen*, 61 USPQ2d 1025, 1027 (B.P.A.I. Aug. 22, 2001) (unpublished).

The B.P.A.I. reversed the rejections asserted by the Examiner and held:

> In responding to [Chen's] arguments, the examiner urges that the level of experimentation is undue and points to the success rate 1% or 20 out of 1746 attempts for the integration of the gene into the embryos described in the specification. However, **the examiner offers no evidence which would**

> **reasonably support a conclusion that one skilled in this art would regard this rate of success for the integration of the rtGH gene as evidencing undue experimentation.** We remind the examiner that some experimentation may be required as long as it is not undue .... [Chen's] **disclosure explicitly describes the methodology** to be used to arrive at the claimed transgenic carp. **As the record now stands, the numbers emphasized by the examiner would reasonably appear to reflect the need for a repetitive procedure, rather than undue experimentation by those wishing to practice the invention.** (*See Ex parte Chen*, 61 USPQ2d 1025, 1028 (B.P.A.I. Aug. 22, 2001) (unpublished); emphasis added.)

The B.P.A.I. found that the Examiner had not established a reasonable basis for questioning the sufficiency of the supporting disclosure when taken in combination with the relevant state of the art as it related to the claimed invention. The B.P.A.I. reversed the scope rejection under 35 U.S.C. §112, first paragraph.

In the present case, as in *Ex parte Chen*, the Examiner has offered no evidence that would reasonably support the conclusion that one skilled in the art would regard the success rate of 2/26 (~7.7%) of obtaining recombinant adenovirus, having the desired characteristics for use in the practice of the methods of present invention, as evidence of undue experimentation. Particularly in view of the fact that applicants have provided a disclosure that explicitly describes the methodology to be used to arrive at the claimed recombinant adenovirus having the desired characteristics for use in the practice of the methods of present invention. The numbers emphasized by the Examiner appear to do no more than reflect that the specification provides a repeatable procedure, rather than undue experimentation, for use by those having ordinary skill in the art to practice the present invention.

Whenever the PTO makes a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *See In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The Examiner has presented no evidence to support the Examiner's questioning of the objective enablement of the claims by the specification. The discussion presented by the Examiner amounts only to conclusions not supported by any evidence or reasoning supported by the current literature.

On the contrary, applicants provided extensive teachings relating to the generation and identification of recombinant adenovirus comprising a single amino acid substitution mutation in the E1B-55K gene that reduces the ability of the mutated E1B-55K protein to bind to the tumor suppressor p53, wherein the recombinant adenovirus retains late viral function. These teachings were discussed in detail herein above. Further, the teachings of the present specification regarding the properties of the claimed recombinant adenoviruses (for example, reduced binding to p53, retention of late viral function and replication in target cells, and tumor cell cytotoxicity) completely support the method claims of the present invention. As discussed above, the reference of Kim, et al., also supports, by comparison to clinical trials of cancer treatments employing ONYX-015, use of the recombinant adenovirus of the present invention in methods of cancer treatment.

The Examiner states that "applicants have elucidated the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26 produced have the recited functional requirements" (*see* Office action, mailed 15 January 2008, page 5). Once again, this statement is merely a conclusion without any evidence to support it. The Examiner has NOT provided any evidence that teaches that finding 2/26 mutants (or 7.7% of recombinant viruses screened) with the desired characteristics constitutes undue experimentation. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). Further, the enablement requirement may be satisfied even though some experimentation is required. *See Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

The Examiner also asserts "[t]he instant rejection is based upon the highly unpredictable nature of the claimed method of treatment of *any* cancer using *any* of a broad genus of adenovirus" (*see* Office action, mailed 15 January 2008, page 6; emphasis in original). This statement mischaracterizes the claims as the claims (i) are not directed to the treatment of "*any* cancer", rather the claims are directed to a method of treating a cancer, characterized by neoplastic cells that substantially lack p53 function, and (ii) are not directed to "*any* of a broad genus of adenovirus," rather the claims are directed to a "recombinant adenovirus comprising a mutation in the E1B-55K gene, said gene encoding a mutated E1B-

55K protein comprising a single amino acid substitution mutation, said single amino acid substitution mutation reducing the ability of said mutated E1B-55K protein to bind to the tumor suppressor p53 when compared to the ability of wild-type E1B-55K protein to bind to the tumor suppressor p53 and said recombinant adenovirus has the further property of retaining late viral function."

The Examiner goes on to assert that "[t]he lack of guidance as to the molecules to be used exacerbates the highly unpredictable nature of treating cancer" (*see* Office action, mailed 15 January 2008, page 6). Once again, however, this is an assertion unsubstantiated by any evidence. Contrary to this assertion the specification provides a great deal of guidance concerning how to make and use the recombinant adenovirus, having the claimed characteristics, in methods of treating cancer, as discussed herein above.

Further, the Examiner asserts "[w]hile one of skill in the art can readily envision numerable species of nucleic acid sequences that have at least a single amino acid mutation in EIB 55k, one cannot predict which of these also generate an adenovirus that treats cancer" (*see* Office action, mailed 15 January 2008, page 6). Once again, however, this is an assertion unsubstantiated by any evidence. Contrary to this assertion the specification provides guidance concerning how to generate the recombinant adenovirus of the present invention (*see, e.g.,* specification, Example 1, pages 17-19), how to identify recombinant adenovirus having a mutated E1B-55K protein with reduced ability to bind to the tumor suppressor p53 when compared to the ability of wild-type E1B-55K protein to bind to the tumor suppressor p53 (*see, e.g.,* specification, Example 2, pages 19-22), how to identify recombinant adenovirus with the property of retaining late viral function (*see, e.g.,* specification, Example 3, pages 22-23), and how to identify recombinant adenovirus with increased killing of neoplastic cells that substantially lack p53 function (*see, e.g.,* specification, Example 4, page 23).

In the Office action, mailed 15 January 2008, the Examiner invokes the holdings of *Amgen Inc.*, *Fiers*, and *Reagents of the Univ. of Calif.* to assert the following:

> an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no

> more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. (*See* Office action, mailed 15 January 2008, pages 6-7; emphasis added.)

First, applicants point out that the present rejection is a scope of enablement rejection under 35 U.S.C. ¶112, first paragraph, NOT a written description rejection. Second, applicants point out that the claims are drawn to recombinant adenovirus having defined properties NOT to an isolated nucleic acid sequence *per se*. Third, regarding "chemical compounds," applicants remind the Examiner of the holding in *In re Papesch* that stated:

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, and the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to identify what is being patented, as the metes and bounds of a deed identify a plot of land, the thing that is patented is not the formula but the compound identified by it. *See The Regents of the University of New Mexico v. Knight and Scallen,* 321 F.3d 1111, 1122, 66 U.S.P.Q.2D 1001 (Fed. Cir. 2003) *citing In re Papesch,* 315 F.2d 381, 391, 137 U.S.P.Q. 43, 51 (CCPA 1962).

How to make and use the recombinant adenovirus having the claimed properties of the present invention is extensively described by the specification as described herein above. Accordingly the Examiner's reliance on the holdings of *Amgen Inc.*, *Fiers*, and *Reagents of the Univ. of Calif.* is improper and does not bear on the claims or the asserted rejection at issue.

Finally, the Examiner asserts the following:

> As to applicants arguments that "it is inappropriate for the Examiner to be questioning the scope of the presently claimed invention based on a question of whether or not one of the ordinary skill in the art is capable of "identifying adenovirus with single amino acid mutations in the El B 55k gene that have lost the ability to bind to p53", this statement omits the central issue

at question which is in the remainder of the rejection "and furthermore be used to treat cancer". (*See* Office action, mailed 15 January 2008, page 7; emphasis added.)

Applicants provided extensive teachings relating to the generation and identification of recombinant adenovirus comprising a single amino acid substitution mutation in the E1B-55K gene that reduces the ability of the mutated E1B-55K protein to bind to the tumor suppressor p53, wherein the recombinant adenovirus retains late viral function. The details of these teachings were discussed herein above. Regarding the use of the recombinant adenovirus in methods of treating cancer, the teachings of the present specification concerning the properties of the claimed recombinant adenoviruses (for example, reduced binding to p53, retention of late viral function and replication in target cells, and tumor cell cytotoxicity) completely support the method claims of the present invention. As discussed above, the reference of Kirn, et al., teaches the use of ONYX-015 in clinical trials for viral therapy of cancer, in particular discussing a potential-synergistic interaction between adenoviral therapy and chemotherapy that has been demonstrated in multiple clinical trials (Kirn, et al., page 6666, col. 1, to 6667, col. 1). In the present application, applicants have consistently compared important phenotypes of ONYX-015 to the replication-selective recombinant adenoviruses of the present invention.

Applicants demonstrated that the recombinant adenoviruses of the present invention (i) showed substantially reduced binding of p53 (as does ONYX-015; *see* specification, Example 2, pages 19-22), (ii) showed protein synthesis profiles more similar to wild-type than to ONYX-015 which is an advantage because generally higher levels of adenoviral replication correspond to increased cytotoxicity in target cells (*see* specification, Example 3, pages 22-23), and, consistent with the previous observation, (iii) tumor cell specific cytolytic activity of the recombinant viruses of the present invention was higher than ONYX-015 (*see* specification, Example 4, page 23). Thus, it is clear from the data presented by applicants that the recombinant viruses of the present invention provide at least similar if not superior anti-cancer properties relative to ONYX-015, which has been demonstrated in clinical trials to be useful for the treatment of cancers.

Accordingly, in view of the above arguments, applicants submit that the Examiner has failed to establish a *prima facie* case for lack of enablement of the present invention due

to undue experimentation.

II. Conclusion.

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 780-9030.

Respectfully submitted,

Date: 15 July 2008 By: Gary R. Fabian

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